(Form to be on hospital headed paper)

THIS TRIAL HAS BEEN REVIEWED AND APPROVED BY A RECOGNISED RESEARCH ETHICS COMMITTEE

INFORMATION SHEET FOR PATIENTS/ VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project: GETAFIX: Glasgow **E**arly **T**reatment **A**rm **F**av**I**piravir^{X}: A randomized controlled study of favipiravir as an early treatment arm in COVID-19 patients

IRAS ID: 283151

<u>This information sheet is for patients who have suspected or confirmed COVID-19</u>

Introduction
We would like to invite you to take part in our research trial. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

Why have I been invited to take part?
You have been invited to take part because you have recently been referred for a test to see if you have a condition called COVID-19. This condition is caused by a virus called SARS-CoV-2, also known as coronavirus. COVID-19 is a new illness which can affect different parts of the body including the lungs and airways. All patients are given supportive care – this means the standard care and treatment that your doctor thinks is best - to manage and treat symptoms of COVID-19. If your test for coronavirus is positive, and your doctor thinks you are suitable for the trial, you will then be considered for entry into the trial if you meet all of the criteria.

Do I have to take part?
No, taking part in the trial is entirely voluntary. It is up to you to decide whether or not to take part. If you *do* decide to take part, you will be given this information sheet to keep and asked to sign a consent form. You are still free to withdraw at any time without giving a reason. This will not affect the quality of care you receive.

If you decide *not* to take part, you will continue to receive the supportive care that your doctor thinks is best for you. Deciding not to take part in the trial will not affect the quality of your treatment in any way. You are free to withdraw your participation in this research study at any time without giving a reason, or this affecting your standard of care. Your doctor may stop your participation in this research study without your consent for medical or other reasons. If you decide to withdraw from the study, data or tissue already collected with your consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to you

If you become so unwell during the course of this study that you are admitted to hospital and lose capacity (for example, you become delirious due to a high temperature), you will be allowed to continue with the study for as long as you are able to swallow the tablets. All other study processes, including safety blood tests, will also continue where possible. No patient, whether they have capacity or not, will be allowed to continue on the study if it is considered unsafe to do so in the opinion of the study doctor, or the independent committee who monitor the trial.

What is the purpose of the trial?
The purpose of this trial is to find out if giving patients an anti-viral drug, favipiravir in addition to supportive care, is more effective than the supportive care alone. The trial is expected to take 6 months to complete, with approximately 300 patients taking part.

What is the drug that is being tested?
The drug being tested is called favipiravir (brand name Avigan). Favipiravir is an anti-viral medicine. It is thought it may help treat COVID-19 by preventing the virus from multiplying in the cells of the body. A shorter treatment course (5 days) of favipiravir has been approved in Japan for the treatment of new strains of influenza (flu). The influenza virus is caused by a different virus so we do not know if favipiravir will be effective against coronavirus. Favipiravir has been used to treat other types of virus, mostly in research studies, but it has not been widely used across the world.

Favipiravir is an oral medication that is given as tablets and taken twice a day. The favipiravir tablets are manufactured in Japan but please be reassured that the medicine has gone through a series of checks to ensure it has been manufactured and handled to the same standard as other medicines available in the UK.

How are treatment options decided?
If you enter the trial, you will be allocated to one of the following treatment arms:

1) Standard treatment as decided by your doctor and clinical team
2) Standard treatment as decided by your doctor and clinical team plus favipiravir

Favipiravir will be given at a dose of 1800mg (9 tablets) twice a day on day 1 of treatment, then 800mg (4 tablets) twice a day from day 2 until day 10. You will take the tablets yourself at home, and record each time you take them in a diary that we will provide. Depending on the set-up of your local clinic, you may be asked to take the first dose there, so that a blood test can be taken afterwards.

Randomisation
You will be assigned to either arm 1) or arm 2) by a process called randomisation. Randomisation is a process where a computer decides randomly which treatment you will receive, like tossing a coin. Neither you nor your doctor will decide which treatment you will receive. You will not be allocated to treatment in line with usual clinical decision-making. You may or may not receive the drug treatment. You have a 50:50 chance of being randomised to receive either treatment 1 or treatment 2.

What will happen to me if I take part?
If you decide to take part in this trial, you will be asked to sign a consent form and will be provided with a copy to keep, along with a copy of this patient information sheet. Before you take part in the trial, your trial doctor/nurse will examine you and ask about your medical history. You will then have the following tests to determine if you can take part:

- Temperature, pulse rate, oxygen saturation, blood pressure, breathing rate
- Height and Weight
- Routine clinical blood tests
- Pregnancy test (for women of childbearing potential)
- Nose and throat swab to test for coronavirus (if not performed already)

Only once you have had all these tests will we be able to confirm whether or not you can take part in the trial. If you are not able to take part, your doctor will advise you on the treatment that you can take as standard care. If you are eligible to enter the trial, you will be allocated to a treatment arm randomly (as described previously).

What happens after I go home?
If you are in the favipiravir group, you will be given instructions on how and when to take your trial medication. We will also ask you to record the times you took your trial medication every day in the diary that we provide. Regardless of which arm of the trial you are in, a member of the trial team will call 1 week into the study (Day 8) to check how you are, and record any new symptoms or medications you have taken.

In both arms of the trial, you will also have further follow-up appointments, Ideally, these would involve coming to a clinic, but if you cannot manage this, we can call you instead and do these over the telephone. Follow-ups will occur at two weeks, one month and two months after starting the trial. If you can come to clinic, the tests you had at screening, including blood tests and nose and throat swabs will be repeated, and you will also be asked to complete a questionnaire. If you are unable to come, we will record some simpler information on how you are doing over the telephone.

What elements of the trial are additional to standard care?
The core elements of the trial that are additional to standard of care, are the provision of Favipiravir (if you are allocated to that arm), the extra follow-up checks (at 1 weeks, 2 weeks, 1 month and 2 months), which all patients will receive. All participants will also have extra blood tests at their screening visit, and some may need to have a diagnostic COVID19 test repeated (a nose and throat swab).

If you have your follow-up checks done over the phone, you will not have further blood tests or swabs. However, if you are able to come to clinic you will have routine bloods re-checked, plus a separate blood sample for research tests (approximately 12 mls (2 teaspoons)) and a repeat nose and throat swab. The repeat swabs are to check your body has cleared the virus.

If you are allocated to the favipiravir arm of the trial, and you are attending a clinic with the required facilities, and you are able to stay for around 2 hours after your consent and randomisation steps have been concluded, we would also like you to have some further blood tests to help us understand how quickly favipiravir gets into your body. This part of the trial

is voluntary and can be omitted if you prefer. It would involve you have an extra 4ml (1 teaspoon) of blood taken before, then 30 and 90 minutes after you take your first tablet.

What elements of standard care may I not receive if I agree to take part in this trial?
There are no elements of standard care that you would not receive if you take part in the trial.

Taking the trial medication
Favipiravir is given orally (by mouth), and is supplied as tablets. Each tablet contains 200mg of favipiravir. On the first day you will be given a loading dose, which means you will receive a higher dose on day 1 than on the following days. On treatment day 1 you will be asked to take 9 tablets (1800mg), and another 9 tablets 12 hours later. On the second day, and for the remainder of your treatment, you will be asked to take 4 tablets (800mg), followed by another 4 tablets 12 hours later. A lower dose will be given if your liver is not working as well as it should. The tablets are round, coated and of medium size (just under 9mm in diameter) so we think most people will be able to swallow them without too much difficulty. Treatment will continue for 10 days, and you will be given all of the tablets you need to complete the course at home. We will also provide you with the following:

- **Alert card:** This contains information on the trial and who to contact in case of an emergency. You should carry the card with you at all times and show it to any doctor, nurse or pharmacist who treats you.
- **Additional information sheet on favipiravir:** This sheet contains important information on how to take the study medicine. Please read this information carefully and ask the study doctor or nurse if you have any questions.
- **GETAFIX Favipiravir Diary:** Use this to record when you take each dose.

Other medicines may influence each other when taken together (interaction). While you are taking favipiravir you will only be able to take a maximum of SIX tablets (3000mg) of paracetamol in 24 hours. The study team will discuss this further with you before you leave hospital but please let the study team know if you start any new medicines, vitamins or supplements during the 10-day favipiravir treatment course. Treatment may be stopped sooner if you do not want to continue, you experience unacceptable side-effects, or if the study doctor thinks it is in your best interests. Treatment will also stop if for any reason you are no longer able to swallow the tablets.

Clinic attendance
You will be asked to attend clinic for an initial screening visit. We would also like to see you for follow-up checks face-to-face, if you are able to attend. However, if you would rather have your checks done over the telephone we can do this, although it does mean we cannot collect repeat swabs to check if the virus has gone, and we cannot perform further blood tests and questionnaires to help us understand everything we can above favipiravir in COVID19. However you would like to have them, follow-up checks will be done around 1 week, 2 weeks, 1 month and 2 months after your first visit.

Pregnancy and breastfeeding
Favipiravir is likely to cause harm to an unborn child and so women who may be in the very early stages of pregnancy or could become pregnant and are not willing or able to use reliable

contraception for 3 months after the last favipiravir dose will not be able to take part in this study. A pregnancy test will be performed in all women who could become pregnant. Women who are breastfeeding will also not be able to take part in the study unless they are willing to stop. Favipiravir has also been found in semen after treatment so men should not father a child or donate sperm whilst taking part in this research.

If you/or your partner are of childbearing potential, and you are sexually active, you must agree to use medically approved contraception throughout your participation in the trial and for at least 3 months after finishing your treatment. If appropriate, your trial doctor will discuss this with you further. If a participant/partner of a participant was to become pregnant within 3 months of completing the trial, then the pregnancy must be reported to the trial doctor/nurse immediately. With your consent, the pregnancy will be followed up by the Clinical Trials Unit Pharmacovigilance department until delivery.

Our approach to pregnancy and breastfeeding is summarised in the following table:

Pregnant or breastfeeding	Not eligible
Female participant has been sexually active without using contraception in the last month	Not eligible due to possibility of early pregnancy (not detected by test)
Women currently taking contraceptives or celibate	Eligible if negative pregnancy test and continue on contraception for 3 months
Men currently using contraceptive or celibate	Eligible if continue on contraception for 3 months

Favipiravir may cause some people to become more sensitive to light and cause a rash or other mild skin reaction. You should avoid strong sunlight or UV light (e.g. a sun bed) during and for 1 week after favipiravir treatment. Remember to cover any sun exposed areas of skin and use sunscreen with high sun protection factor (SPF).

What will be the side effects of any treatment I receive in this trial?

As well as possible benefits, trial medicines can also produce side effects. The information we currently have on Favipiravir suggest that most patients do not get side-effects but up to 1 in 5 patients may experience at least one side-effect. Importantly, these are generally minor and stop when you stop taking the tablets. Favipiravir has already been licensed in other countries for treatment of influenza. In the table overleaf we have summarised the most common side-effects reported by 1653 patients who received a shorter (5-day) course for this reason.

SIDE-EFFECTS FROM FAVIPIRAVIR IN 1653 PATIENTS	Percentage of patients (%)
Symptoms	
Diarrhoea	2.3%
Feeling sick (nausea)	2.1%
Being sick (vomiting)	1.0%
Urinary tract infection	1.5%
Headache	1.1%
Changes in Blood Tests	

Higher levels of triglycerides (a blood fat)	1.9%
Higher level of ALT and AST (proteins made by the liver)	1.9% & 1.3% respectively

Other uncommon side effects reported in smaller studies include the following:

- changes in the numbers of some types of cells in the blood, including white blood cells
- higher levels of uric acid, which is produced by normal processes in the body and removed by the kidneys
- increases in other liver proteins
- reduction of blood potassium (a blood salt)
- effects on the skin such as rash and itch
- unusual behaviour and dizziness
- nose bleeds
- upper abdominal pain

A study of approximately 130 patients used a higher dose than will be used in this study also showed no severe side effects. However not all side effects are known and other serious side effects that are more long lasting have occurred with medicines similar to favipiravir. If you suffer from something that you think may be related to your treatment within this trial, please contact your trial doctor or research nurse. You will be monitored closely for these and any as yet unknown side effects while you are in hospital and taking the study medicine.

What are the possible disadvantages and risks of taking part?

If you are randomised to receive the trial medicine, you may experience the side effects of this drug that are discussed above. There is also a small chance that you may have a severe reaction, such as an allergic reaction. You will be monitored closely and may need to take additional treatment to control any side effects that develop. However, you can stop the trial treatment at any time if you or your doctor feels that the side effects are a problem for you. Stopping the trial treatment will not adversely affect your further care in any way. Information on side effects and the treatment of side effects will be closely monitored by doctors involved in the trial. In addition, the trial will be carefully monitored by an independent group of experts who will regularly advise the doctors about the safety of the trial.

What are the possible benefits of taking part?

We are conducting the trial because we believe that Favipiravir may improve outcomes from COVID19. However, this may not prove to be correct, and even if it is, and you are allocated to receive Favipiravir, there may not be direct medical benefits to you. However, the information gained will help improve our understanding of COVID-19 treatments for future patients.

What is the usual treatment for COVID-19?

New information on treatment of COVID-19 is becoming available all the time and new medicines or therapies may become available during the period of this study. The study team will provide you with up-to-date information about other possible treatment options that might be available to you when they discuss this trial with you.

What are the alternative treatments?
The only alternative treatment for mild COVID19 is supportive care, including pain killers and medicines for fever. Your doctor can explain these if required and you would receive this in the trial whichever arm you are allocated to.

Can I still receive the COVID-19 vaccine?
Yes - you can still receive a UK Government approved COVID-19 vaccination during the 60-day trial period. If you do receive a vaccine during this time, please inform the study nurse or doctor at your next follow-up visit or phone call.

What if new information becomes available?
Sometimes during the course of a trial, new information becomes available about the treatment that is being studied. If this happens, your trial doctor will tell you about it and discuss with you whether you want to continue in the trial. If you decide to withdraw, your trial doctor will make arrangements for your care to continue. If you decide to continue you may be asked to sign an updated consent form. Also, on receiving new information your trial doctor might consider it to be in your best interests to withdraw you from the trial. If this happens, he/she will explain the reasons and arrange for your care to continue.

What if something goes wrong?
If you have a concern about any aspect of this trial, you should ask to speak with the trial doctor or nurse who will do their best to answer your questions. The trial Sponsors have responsibility for ensuring that financial cover for damages or compensation arising from 'no fault' harm is available to patients, where applicable. In the event that something does go wrong, and you are harmed during the research and this is due to someone's negligence, then you may have grounds for a legal action for compensation but you may have to pay your legal costs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this trial, the normal National Health Service complaints mechanism will still be available to you. If you do have a complaint, then please contact *(Insert local complaint department details here including contact name, number and address prior to printing patient information sheet on local headed paper).* Participating in this study may affect any insurance cover you have (e.g. travel insurance, protection insurance (life insurance, income protection, critical illness cover and private medical insurance).

Will my taking part in the trial be kept confidential?
Any data collected during this trial and any of the results published will not identify you personally. Your medical records will only be available to the trial doctors, your hospital consultant, responsible individuals from the Clinical Trials Unit, Glasgow, the trial Sponsor(s), and the regulatory authorities. Your information may also be looked at by personnel from Fujifilm, the pharmaceutical company that manufacture and supply the drug. The purpose of this would be to check that the trial is being carried out correctly.

We will inform your General practitioner (GP) if you participate in this trial, including details of your diagnosis, and an overview of the trial and the study treatment. Contact details will be given to your GP in case they have questions or concerns at any time.

The Clinical Trials Unit (Glasgow), which are coordinating the trial, will collect your initials, date of birth and Community Health Index (CHI) number. This information will be stored securely and will be kept confidential, with access provided only to authorised personnel. NHS Greater Glasgow & Clyde and the University of Glasgow are the co-sponsors for this study. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The Co-Sponsors will keep identifiable information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information https://www.hra.nhs.uk/information-about-patients/

Your consent for participation in this trial also includes your consent to allow the use of the data in your medical/clinical record to be used for the purposes of future research. As there is a worldwide need to develop new treatments for COVID-19, it is possible that we may combine data from the GETAFIX trial with data from another study in order to get the most meaningful and useful results. All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and UK applicable laws to ensure your confidentiality is maintained.

What will happen to any samples I give?

Blood samples will be taken to monitor your progress. If you are taking favipiravir they may also be taken to check for side effects and to check levels of the drug in your body. You will also be asked to consent to provide additional blood samples for research purposes. These samples will be sent to collaborating laboratories and will be used for other ethically approved and relevant investigations, conducted by qualified researchers. These studies may include analysis of genetic material (DNA). The nose and throat swabs that you provide will be sent to a laboratory to check for coronavirus. An additional test will also be done on these swabs to find out the amount of coronavirus that is present.

What will happen to the results of the trial?

When the trial ends, the results will be analysed and presented at national and international scientific conferences and published in a medical journal. The results will also be published on selected websites. The confidentiality of all patients will be maintained. You will not be personally identified in any reports or publications resulting from the trial. If you would like to obtain a copy of the published results, please ask your trial doctor.

Who is organising and funding this research?

The trial is being co-sponsored by NHS Greater Glasgow and Clyde and the University of Glasgow and is being co-ordinated by one the Clinical Trials Units in Glasgow, which is based at the Gartnavel campus. Financial support will be provided by The Chief Scientist Office, Scotland. None of the doctors or other staff conducting the research are being paid directly

for recruiting patients into the trial. You will not be paid for taking part in this trial, but reasonable travel expenses for hospital/clinic visits will be reimbursed (up to £20 per patient per visit). Your study nurse will advise you on how to claim this.

Who has reviewed this trial?
This trial has been reviewed by a number of medical specialists during its development. The trial has also been reviewed and approved by the Sponsor's Research and Development Department and the Health Research Authority (HRA) Research Ethics Service A Glasgow confirm that the trial respects patients' rights and the protection of patients' health. This trial will comply with current government, health board, MHRA and HRA guidance regarding COVID-19.
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Contact for further information
If you have further questions about your illness or about clinical studies, please discuss them with your trial doctor. If you have any questions about your rights as a patients in this study you may want to contact your Advice and Liaison Service Office > Please insert local details on telephone number < Please insert local details>

If during the course of the trial you have any questions regarding your participation or would like further trial specific information before making your decision please contact:

Doctor:	*Name Insert*
Telephone Number	*Number insert*
Research Nurse:	*Name Insert*
Telephone Number	*Number insert*
24-Hour / out of hours contact:	*Insert local details*

You will be provided with a copy of this information sheet and a copy of your signed consent form to keep (depending on current guidelines regarding paper leaving COVID-19 wards, you may be provided with this following your inpatient stay or have this emailed). You should keep this information in a safe place and in your possession for as long as you are in the study.

During the study, if there is an emergency please do what you would routinely have done and inform your study doctor on the telephone number given at the end of this form as soon as possible. Should you have to visit another doctor tell him/her that you are taking part in this study so that he/she can contact your study doctor if necessary.
If you find the wording difficult to understand or would like us to explain things to you once more, please feel free to ask your doctor or nurse.

Thank you for taking the time to read this information sheet. If you wish to take part you will be given a copy of this information sheet and a signed consent form to keep.

(Form to be on hospital headed paper)

CONSENT FORM FOR PATIENTS/ VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Patient Identification Number for this trial:
(to be obtained post randomisation)

Title of Project:
GETAFIX - Glasgow **E**arly **T**reatment **A**rm **Favipiravir**$^{\chi}$: A randomised controlled study of favipiravir as an early treatment arm in COVID-19 patients

IRAS ID: 283151 **Please initial box**

1. I confirm that I have read and understand the patient information sheet Version 6, dated 15th June 2021 for the above trial, that I fully understand what is involved in taking part in this trial, and that I have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree that relevant sections of any of my medical notes and data collected during the trial may be looked at by responsible individuals from the Clinical Trials Unit (NHS Greater Glasgow & Clyde), the trial Sponsors, the regulatory authorities, the NHS organisation and personnel from Fujifilm where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. I give my permission for a letter and information regarding my participation in this trial to be sent to my GP. ☐

6. I agree to take part in the above trial. ☐

7. I give my permission to give extra samples of blood for laboratory research purposes and to be kept for future research as described in the information sheet for the above trial. I understand how the samples will be collected, that giving samples is voluntary and that I'm free to withdraw my approval for use of the samples at any time ☐

without giving a reason and without my medical care or legal rights being affected.

8. I give my permission for samples from nasopharyngeal swabs to be collected and used for future laboratory research purposes as described in the information sheet for the above trial. I understand how the sample will be collected, that giving samples is voluntary and that I'm free to withdraw my approval for use of the samples at any time without giving a reason and without my medical care or legal rights being affected. ☐

***Please sign and date below**:*

Name of Patient	**Date**	**Signature**

Name of Person taking consent	**Date**	**Signature**

WITNESS CONSENT

Where the participant is unable to read the text and/or sign for themselves, but has capacity to give consent:

Please initial box

I witnessed accurate reading of the consent form to the potential participant, who could ask any questions and got satisfactory replies. ☐

I confirm the participant gave consent freely to points 1 -8 above ☐

***Please sign and date below**:*

Name of Witness	**Date**	**Signature**

Name of Person taking consent	**Date**	**Signature**

When completed, 1 original for researcher; 1 original or photocopy for patient; 1 original or photocopy to be kept with hospital notes